The Risk of Childhood Cancer from Intrauterine and Preconceptional Exposure to Ionizing Radiation

Richard Wakeford

British Nuclear Fuels plc, Risley, Warrington, Cheshire WA3 6AS UK

The findings of studies investigating whether exposures to ionizing radiation before birth, either pre- or post-conception, increase the risk of childhood cancer have provoked much scientific controversy. An epidemiological association between the abdominal exposure of pregnant women to diagnostic X-rays and childhood cancer was first reported in the 1950s, while an association between the recorded dose of radiation received occupationally by fathers before the conception of their offspring and childhood leukemia was reported only recently in 1990. The scientific interpretation of these particular statistical associations is by no means straightforward, but the latest analyses of intrauterine irradiation and childhood cancer indicate that a causal inference is likely. Scientific committees have adopted risk coefficients for the intrauterine exposure of somatic tissues, which for childhood leukemia are comparable to those accepted for exposure in infancy, although questions remain about the level of risk of childhood solid tumors imparted by exposure to radiation *in utero* and shortly after birth. In contrast, the association between paternal preconceptional radiation dose and childhood leukemia has not been confirmed by studies using objectively determined doses. The original association has been found to be restricted to children born in one village, it does not extend to cancers other than leukemia, and it is markedly inconsistent with the established body of knowledge on radiation-induced hereditary disease. A causal interpretation of this association has effectively been abandoned by scientific authorities.
Key words: causal inference, childhood cancer, childhood leukemia, intrauterine exposures, ionizing radiation, preconceptional exposures, radiation epidemiology, radiation risks. *Environ Health Perspect* 103:1018–1025 (1995)

In a recent wide-ranging review of adverse health effects after exposure to low levels of ionizing radiation, Nussbaum and Köhnlein (*1*) drew attention to the results of various epidemiological studies of childhood cancer, particularly leukemia, among individuals exposed to radiation before birth, both pre- and post-conception. These results were used to suggest carcinogenic risk coefficients (risks per unit radiation dose), which were appreciably larger than those adopted by national and international scientific bodies, implying that the risks associated with such irradiation have been underestimated for the purposes of radiological protection. Much scientific evidence on this subject has recently become available, and the aim of this review is to determine whether the inferences of Nussbaum and Köhnlein (*1*) concerning these particular exposures can be sustained in the light of this additional information.

Intrauterine Irradiation

A positive statistical association between diagnostic abdominal X-ray exposure of pregnant women and cancer in children was first reported in the 1950s from the Oxford Survey of Childhood Cancers (OSCC), a continuing case–control study of cancer deaths occurring among children under 16 years of age in Britain (*2–5*). The interpretation of this association has been the subject of considerable scientific debate over the years (*6,7*). The most recent analysis of OSCC data, covering nearly 15,000 deaths between 1953 and 1979, suggests an excess relative risk associated with an intrauterine X-ray examination of about 40% (*8*).

Many other studies of *in utero* irradiation and childhood cancer have been conducted, including a large case–control study of approximately 1300 cancer deaths among those under 20 years of age born during 1947–1960 in the northeastern United States (*9,10*). The case–control studies have produced a reasonably consistent picture of positive associations; Bithell (*11*) has calculated the weighted average of the relative risks obtained from all the published studies except the OSCC to be 1.37 (95% CI, 1.26–1.49); if the OSCC is included, the weighted average is 1.39 (95% CI, 1.33–1.45). The association has not been confirmed by cohort studies, including the follow-up of almost 40,000 British children who were X-rayed *in utero* (*12*), although one of the authors of this study has since expressed doubts over the completeness of follow-up (*13*). However, the statistical power of these cohort studies has generally been insufficient to exclude excess relative risks of the magnitude suggested by the case–control studies (*11*).

Uncertainties regarding the accuracy of X-ray examination reports based on recall of mothers have largely been resolved through the use of contemporary medical records (*5,9,14*). Possible confounding factors related to both the X-raying of pregnant women and childhood cancer (primarily those concerned with maternal illness) have been addressed through studies of twins X-rayed (at a higher frequency than singleton births) predominantly for obstetric purposes and not for reasons involving the general health of the mother. The case–control studies that have been confined to twins have produced excess relative risks of childhood cancer associated with an intrauterine X-ray examination comparable to those for singleton births, despite the differing frequencies of such examinations (*15–17*). It should be noted, however, that twins in general experience a rate of childhood cancer which is similar to, if not lower than, that for singleton births (*15,18,19*), although it is unlikely that an excess risk due to fetal X-ray examinations of the magnitude expected could be detected in the twin follow-up studies reported so far (*19*). There is no indication that an increased frequency of postnatal X-rays might account for the findings for twins (*17*), or generally (*20*). Later studies have also considered the effects of other potential confounding factors such as maternal age (*5,10*).

Bithell (*11*) has shown that, because of its size, by far the most informative study of intrauterine irradiation and childhood cancer is the OSCC, and much of the detail of the association has been derived from this study. An appropriate (i.e., linear) exposure–response relationship was originally demonstrated in an analysis of the OSCC data by Stewart and Kneale (*4*) in terms of the number of X-ray exposures, or films, used in an obstetric examination. This exposure–response relationship was not confirmed by a later analysis of the OSCC data (*21*), but Bithell (*11*) has questioned the appropriateness of this particular analysis, demonstrating that a linear exposure–response relationship may still be derived from the OSCC data. [Mole (*22*) has noted that multiple examinations during a pregnancy do not seem to have been taken into account in any of these

I am most grateful to Sir Richard Doll and Colin Muirhead for commenting on this article. I thank Chris Beresford for typing the manuscript.
Received 12 April 1995; accepted 19 July 1995.

analyses.] Mole (*22*) investigated the fetal doses received during various X-ray procedures and concluded that a fixed estimate of the radiation dose per X-ray exposure could not be assumed. Consequently, whether or not an appropriate dose–response relationship exists is equivocal, although a linear dependence between exposure and relative risk would certainly support such a relationship. Further, the magnitude of the relative risk has decreased with calendar year of birth, which is consistent with the reduction in the dose per X-ray examination with time (*11,22,23*), indicating an underlying rising gradient of risk with dose.

Experimental studies using animals, primarily rodents, irradiated *in utero* have not produced consistent evidence for a carcinogenic effect (*24*). However, recent information on dogs irradiated at various stages of development confirms an excess incidence of cancers among young dogs irradiated just before or just after birth (*25*).

Given that ionizing radiation is an established cause of cancer when irradiation occurs postnatally, it would be anticipated from the evidence outlined above that the epidemiological association between intrauterine exposure to diagnostic X-rays and childhood cancer would be interpreted causally. Even though the average fetal dose per X-ray examination is low [around 0.5–5 cGy (*26*)], under the assumption of a no-threshold dose–response relationship, the carcinogenic effect of such doses should be capable of detection, given a study of sufficient size. However, objections to a causal interpretation have been raised, and these have been highlighted by MacMahon (*27*) (the principal investigator in the case–control study conducted in the northeastern United States) and by Miller (*28*).

MacMahon (*27*) points to three reasons the association between irradiation and childhood cancer should be interpreted with caution. First, the absolute risk coefficient derived from the association between childhood cancer and diagnostic intrauterine irradiation is about an order of magnitude greater than the equivalent coefficient derived from assessments of exposure in early childhood, a difference that is difficult to explain biologically. Second, there was no evidence for an excess risk of cancer among children irradiated *in utero* in the atomic bombings of Hiroshima and Nagasaki, even though these individuals received, on average, doses several times greater than those exposed *in utero* to diagnostic irradiation. Third, there is a similar elevation of relative risk associated with *in utero* diagnostic X-ray exposure across all the major groups of childhood cancer, which is uncharacteristic of other exposures.

Knox et al. (*23*), in an analysis of the latest update of the OSCC database, derived an excess absolute childhood (0–14 years of age) cancer mortality risk coefficient of 20.2% (95% CI, 5.5%–29.0%) per Gy [cited by Nussbaum and Köhnlein (*1*)], which is substantially in excess of the equivalent risk coefficient accepted for the irradiation of young children, as indicated by MacMahon (*27*). However, Bithell (*11*) questioned the validity of this analysis, and Muirhead and Kneale (*8*) pointed out that an inappropriate assumption was implicit in the analysis of Knox et al. (*23*) which led, in particular, to the excess relative risk associated with births in 1950 being attributed to the lower average radiation dose per X-ray examination received by those born in 1960. When this was corrected, an absolute risk coefficient for childhood cancer incidence of 13.6% (95% CI, 10.0%–18.4%) per Gy was obtained (*8*). Further, the source of the mean doses per unit X-ray film used to derive this risk coefficient (*4*) is somewhat obscure (*22*), and if the mean fetal doses per obstetric X-ray film presented in the 1972 Report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (*29*) are used instead, the absolute risk coefficient reduces to 6.4% (95% CI, 4.1%–10.0%) per Gy (*8*). Muirhead and Kneale (*8*) emphasize that these confidence intervals do not make full allowance for uncertainties in the dose estimates or in the form of the relative risk model. The excess relative risk would appear to be greatest at the age of 2–6 years, and then decrease markedly at older ages (*8*), which is compatible with the findings of Monson and MacMahon (*10*).

These risk coefficients are derived from analyses of the OSCC data, which make use of all exposures in all trimesters of pregnancy. Gilman et al. (*21*) have suggested that the cancer risk due to irradiation in the first trimester is 2.7 times that due to irradiation in the second and third trimesters; but most of the available data are for exposures later in pregnancy: more than 90% of the information comes from third-trimester obstetric radiography (*21*). Moreover, many of the exposures in the first trimester were carried out for nonobstetric reasons and occurred in the earlier years covered by the study, and these exposures (e.g., fluoroscopy) could well be associated with higher doses than those received during obstetric examinations (*22*). As a consequence, it is unclear from epidemiological data whether the risk coefficient for irradiation early in pregnancy differs from that for third trimester obstetric X-raying.

Bithell and Stiller (*30*), in their analysis of the OSCC data, preferred to adopt the UNSCEAR fetal doses, since the dosimetry scheme (*4*) used by Knox et al. (*23*) could not be reconciled with the rate of the temporal decline of relative risk apparent in the OSCC data. When restricting the analysis to the least uncertain data for third trimester exposures, they derived an absolute childhood cancer risk coefficient of 4.5% (95% CI, 2.7%–6.9%) per Gy (*30*). Under the assumption that the same excess relative risk coefficient applies to all the major types of childhood cancer (*5*), an absolute childhood leukemia risk coefficient of 1.6% (95% CI, 1.0%–2.4%) per Gy is obtained.

Mole (*22*) has argued that the only reliable estimates of fetal doses that can be applied to the OSCC data are those made during the comprehensive investigations of the Adrian Committee in 1958. Applying these fetal dose estimates for third-trimester obstetric exposures to births in the OSCC database during 1958–1961 (the average fetal whole-body dose per obstetric examination being 6.1 mGy), Mole obtained an excess relative risk coefficient of 0.038 (95% CI, 0.007–0.079) per mGy for childhood cancer, giving an absolute risk coefficient of 6.0% (95% CI, 1.0%–12.6%) per Gy. The absolute risk coefficient for childhood leukemia is 2.1% (95% CI, 0.4%–4.4%) per Gy.

Recently, Bithell (*31*) used a model he previously derived (*11*) to describe the variation of the relative risk of intrauterine irradiation with year of birth, in combination with the average fetal dose obtained by Mole (*22*) from the Adrian Committee data. From the model, the excess relative risk associated with X-ray examinations in 1958 is 0.31 (95% CI, 0.17–0.46), and the average fetal dose during this year is 6.1 mGy. This leads to absolute risk coefficients of 8.1% (95% CI, 4.5%–12.1%) per Gy for childhood cancer, and 2.8% (95% CI, 1.6%–4.2%) per Gy for childhood leukemia, although these are likely to be slight overestimates because nonobstetric examinations were included in the risk model. Bithell (*31*) emphasizes the difficulties in obtaining accurate risk coefficients from obstetric X-ray data and suggests that even the most recent estimates could still be wrong by a substantial factor.

Of those Japanese who were *in utero* at the time of the atomic bombings of Hiroshima and Nagasaki in August 1945, 1263 survivors could be followed completely from birth to their 15th birthday (*32*). The average dose received from the explosions by this cohort is 184 mGy, with 753 of the individual doses being at least 10 mGy. As

noted by MacMahon (*27*), this average dose is substantially in excess of that estimated to have been received by fetuses from diagnostic irradiation. Among this cohort, 2 cases of cancer (not leukemia) occurred in individuals less than 15 years of age, who both received doses in excess of 300 mGy. The number of childhood cancer cases expected from Japanese national data is at most 0.73 (*32*), giving an excess absolute risk coefficient of 0.5% (95% CI, -0.2%–2.4%) per Gy. As no cases of childhood leukemia were diagnosed among the Japanese exposed *in utero*, assuming that (at most) half of the expected number of childhood cancers is due to leukemia (*32*), an upper 95% confidence limit of around 1.1% per Gy may be derived from this group for the absolute childhood leukemia risk coefficient.

It is unlikely that the childhood cancer risk coefficients obtained directly from the Japanese survivors irradiated *in utero* will change substantially. Doses currently in use are DS86 uterine doses rather than fetal doses (*32*), and neutron doses for those in Hiroshima may be revised upwards (*33*), but it is difficult to see how final fetal doses will have a major impact on these coefficients. It should be noted that no cases of cancer were recorded among the intrauterine-exposed survivors during the period August 1945–September 1950. Data for this early period are inevitably less certain (*32*), and analysis of the OSCC data set has shown that the excess relative risk of childhood cancer associated with diagnostic X-ray exposure is greater for the 0- to 4-year age group than for the 5- to 14-year age group (*8*). Mole (*22*) has argued that cell sterilization induced by high doses received during the atomic bombings needs to be taken into account, and that this would have the effect of at least doubling the risk coefficients derived directly from the experience of the Japanese irradiated *in utero*. On the other hand, it is conventional to reduce the risk coefficients derived from high-dose/high-dose-rate studies when extrapolating to low dose/low-dose-rate conditions (*34*). So, whether there is a genuine incompatibility between the level of radiation-induced childhood cancer risk among the Japanese bomb survivors irradiated *in utero* and that arising from fetal exposure to obstetric X-rays is unclear, given the remaining uncertainties in both data sets. However, what is clear is that any discrepancy is unlikely to be as great as that suggested by the childhood cancer mortality risk coefficient of 20% per Gy derived by Knox et al. (*23*) and cited by Nussbaum and Köhnlein (*1*).

It should be noted that a case–control study of leukemia in Utah and radioactive fallout from nuclear weapons testing in Nevada found an association between childhood acute leukemia and irradiation in childhood (consistent with the experience of the Japanese atomic bomb survivors). An association was not observed for subjects *in utero* at the time of the peak exposure to fallout (*35*), although because of the small numbers involved, this finding is unlikely to be incompatible with the risk coefficients derived from medical exposures. Similarly, a study of childhood leukemia in the Nordic countries in relation to fallout from atmospheric nuclear weapons testing (*36*) found some evidence for an excess risk due to irradiation in childhood, at a level anticipated from high-dose studies, but not for intrauterine irradiation. However, since the average fetal dose during the period of highest fallout was assessed to be 0.14 mSv (*36*), it is unlikely that the excess risk due to this exposure could be discerned statistically.

On the basis of the latest results from analyses of the OSCC data, the UK National Radiological Protection Board (NRPB), while recognizing the uncertainties in fetal doses, has assumed an absolute risk coefficient for cancer in childhood (0–14 years of age) following intrauterine irradiation of 6% per Gy (half of these excess cases resulting in death), taken to apply to all trimesters of pregnancy, of which leukemia makes up 2.5% per Gy (again, half the cases being fatal) (*34*). This is consistent with the risk coefficient presented in the BEIR V report of 2.0% to 2.5% per Gy for death from cancer in the first 10 years of life (*26*). It is of interest to compare this leukemia risk coefficient of 2.5% per Gy with that adopted by the NRPB for irradiation in early childhood (*34*), which is based on the BEIR V relative risk model derived principally from the Japanese bomb survivor data (*26*). For a 10-mGy dose received just after birth, the excess absolute risk coefficient for leukemia occurring before the age of 15 years is 1.8% per Gy which, given the inherent uncertainties, is in good agreement with the childhood leukemia risk coefficient associated with *in utero* irradiation.

Of greater difficulty is the third objection to a causal interpretation of the childhood cancer and *in utero* irradiation association raised by MacMahon (*27*), that similar relative risks are found for all the major groups of childhood cancer. This is not the case for cancers (mainly arising beyond the age of 15 years) among the Japanese bomb survivors irradiated in early childhood (*26*) and leads to a considerable discrepancy between the risk coefficients for childhood solid tumors following either intrauterine or infant exposure, the *in utero* exposure coefficient being much higher.

In 1975, Bithell and Stewart (*5*) presented relative risks, derived from the OSCC data, for the major types of childhood cancers which showed that the excess risk associated with *in utero* irradiation was generally uniform across the groupings. Information in this detail has not been presented since then, although more recent reports have indicated similarly raised relative risks for childhood leukemia and grouped solid tumors (*7,23*). In contrast, Monson and MacMahon (*10*), in the latest analysis of data from the northeastern United States, found a significantly raised relative risk of leukemia of 1.52 (95% CI, 1.18–1.95) but not of solid tumors (relative risk 1.27; 95% CI, 0.95–1.70). However, this solid tumor relative risk is not statistically incompatible with that given by Bithell and Stewart (*5*) of 1.47 (95% CI, 1.31–1.66).

It is undoubtedly the case that the cancers of childhood are, in general, quite different from those of adults, and it may be that models derived [e.g., by BEIR V (*26*)] primarily from the study of adults are not appropriate for childhood solid tumors, particularly concerning a 10-year minimum latency. In this respect, it is of interest that experimental studies have shown differences in tumor types in animals irradiated either *in utero* or postnatally (*24*). Further, information on the risk of childhood cancer from those irradiated early in postnatal life is limited (*34*), so the risk coefficient for childhood solid tumors obtained from fetal irradiation studies is not necessarily inconsistent with the findings of studies of postnatally exposed individuals, and the *in utero* exposure risk coefficient for childhood solid tumors may be the most appropriate to apply to exposures in early childhood. Certainly it is known that the relative risk coefficient for adult solid tumors is greater for younger ages at exposure (*34*), so this would not be implausible. However, this is an outstanding issue which requires resolution. Even so, were the risk coefficient for childhood solid tumors derived from studies of intrauterine exposure to diagnostic X-rays to be adopted for irradiation in early childhood, this would have only a minor impact on population risk coefficients, since these are dominated by the risk coefficients for adult cancers.

Apart from this last point, the difficulties in reconciling the findings of the case–control studies of childhood cancer and fetal exposure to diagnostic X-rays with the body of knowledge concerning radiation carcinogenesis have largely disap-

peared, due mainly to the results of more recent studies. The risk coefficients associated with intrauterine irradiation adopted by authorities such as NRPB and BEIR V are quite compatible with (and, indeed, are based on) the OSCC data, contrary to the suggestion of Nussbaum and Köhnlein (*1*).

Preconceptional Irradiation

Nussbaum and Köhnlein (*1*) discussed the possible risk of childhood cancer, particularly leukemia, arising from preconceptional irradiation, noting the important implications of this putative risk for radiological protection and for radiobiology.

In 1984, the Independent Advisory Group confirmed a media report of an excess of childhood leukemia in the coastal village of Seascale, adjacent to the Sellafield nuclear complex in West Cumbria, England (*37*). The group could find no causal link between radioactive discharges from Sellafield and the leukemia cases, but recommended that further research be carried out, including a case–control study. In 1990, Gardner et al. (*38*) reported the preliminary results from the West Cumbria leukemia and lymphoma case–control study, which examined a wide range of factors possibly linked to the Seascale excess. The most striking findings were associations between relatively high doses of ionizing radiation measured by film badges worn by men employed at Sellafield before the conception of their children, and the incidence of leukemia in these children. The authors suggested that this association was sufficient to account for the childhood leukemia cases in Seascale (*39*).

Gardner et al. reported associations both with a cumulative preconceptional dose of ≥100 mSv and with a dose of ≥10 mSv received in the 6 months preceding conception, although these doses were highly correlated (*38,40*). Doses were based on annual summaries of individual recorded external whole-body doses, and the average doses for the highest dose categories were around 200 mSv and 20 mSv, respectively. Relative risks of 6–8 were found, although because these were based upon (the same) four cases and a similarly small number of controls, lower 95% confidence limits were less than 2. An appropriate dose–response relationship was suggested only by the 6-month dose association. Similar associations were also found for childhood leukemia and non-Hodgkin's lymphoma combined, but the results were driven by cases of leukemia.

These findings were unexpected, as there was no previous reliable evidence for paternal preconceptional irradiation and increasing the risk of childhood leukemia, particularly to the extent suggested by these results (*41–43*). However, the proposed explanation for the Seascale leukemia cases was attractive because of the failure of other factors to account for the excess, including exposure of somatic tissues to sources of environmental radiation (*39*).

The findings of Gardner et al. initiated considerable scientific activity. Another excess of childhood leukemia had previously been reported from near the Dounreay nuclear installation in northern Scotland, and a case–control study of these cases was already underway when Gardner et al. published their findings. The results were reported in 1991 (*44*), and no association between paternal preconceptional radiation dose and childhood leukemia and non-Hodgkin's lymphoma was found, although the study was small and the findings were not incompatible with those of Gardner et al. (*45*). However, this study did demonstrate that the excess of childhood leukemia near Dounreay could not be explained by factors associated with paternal employment in the nuclear industry before conception, including radiation exposure.

Another case–control study commenced in the 1980s to investigate an excess of leukemia in young children living near the Aldermaston and Burghfield nuclear weapons facilities in West Berkshire, England. In 1993, the results of this study were published (*46*). An association with fathers being monitored for external radiation exposure in the preconceptional period was found (based on three cases and two controls with exposed fathers), but since recorded doses were low (<5 mSv), there was no association with radiation dose. Interestingly, in an equivalent comparison, Gardner et al. found no association with being monitored for external radiation exposure (RR = 1.09, 95% CI, 0.45–2.66) (*40*). However, Roman et al. (*46*) speculated as to whether this association with radiation film badge issue might be indicative of internal radioactive contamination or of some other occupational exposure. Paternal preconceptional employment in the nuclear industry could not account for the childhood leukemia excess in the Aldermaston and Burghfield area.

The results of a further study in progress at the time of the report of Gardner et al. were published in 1991 (*47*). This case–control study examined three areas in northern England where raised levels of childhood leukemia had been reported, including part of West Cumbria. Owing to a large degree of overlap with the study of Gardner et al. [only one case with a recorded paternal preconceptional dose (a total dose of 1 mSv) was not included in the data of Gardner et al.] this study offers little in the way of independent evidence (*48*).

A review of epidemiological studies of preconceptional irradiation reported before 1989 identified only one study which found an association between paternal preconceptional radiation exposure and childhood cancer or leukemia (*49*). Shu et al. (*50*) conducted a case–control study of childhood leukemia in Shanghai during 1974–1986 and found an association between childhood leukemia and the number of preconceptional X-ray exposures received by the father, as reported at interview. No similar association was found for reported maternal X-ray exposures. However, exposure information for over 80% of fathers was supplied by mothers at interview. In a subsequent case–control study carried out by Shu et al. (*51*) of childhood leukemia in Shanghai during 1986-1991, in which both mothers and fathers were interviewed, the association between childhood leukemia and paternal preconceptional X-ray exposure was not confirmed, indicating that the original association was probably due to recall bias. Recently, however, Shu et al. (*52*) have published the results of a case–control study of infant (0–18 months of age) leukemia in North America during 1983–1988. Associations between infant leukemia and paternal preconceptional exposures of the abdomen to diagnostic X-rays were found, and weaker associations were found with chest and limb exposures. No similar associations were reported for maternal preconceptional X-ray exposures. Exposure data were based entirely on information reported by parents at interview. Of parents who refused to participate in the study, about twice as many were control parents as case parents, and of the participants, about twice the number of control fathers refused to be interviewed compared with case fathers, which could be indicative of potential bias.

Shiono et al. (*53*) reported an association between cancer in young children and maternal preconceptional X-ray exposure in a case–control study nested within a cohort of children born during 1959–1965 across the United States, the reported exposure data being collected prospectively. However, the point estimate of the relative risk for leukemia and lymphoma cases alone was less than that for all cancer cases, and did not differ significantly from 1.0 (C.S. Chung, personal communication). Graham et al. (*20*) found an association between childhood leukemia and maternal preconceptional X-ray exposure in a case–control

study of childhood leukemia in three areas of the United States during 1959–1962. In a comparison of medical records with X-ray exposures reported at interview, considerable discrepancy was found (*54*). Even when using exposure data from medical records, appreciable uncertainty must remain because these records could only be accessed for physicians, dentists, and hospitals mentioned at interview (*54*). In an analysis of OSCC data, Kneale and Stewart (*55*) found no support for preconceptional (either maternal or paternal) X-ray exposure increasing the risk of childhood cancer once biased recall had been taken into account.

Yoshimoto et al. (*56*) confirmed the absence of any excess risk of childhood cancer and leukemia among over 30,000 offspring of Japanese survivors of the atomic bombings of Hiroshima and Nagasaki who received a dose in excess of 10 mSv. The average preconceptional dose received by exposed fathers was 418 mSv. The findings of Gardner et al. concerning cumulative paternal preconceptional irradiation are incompatible with the absence of an excess leukemia risk among the Japanese children, whether paternal or joint parental doses are considered (*57–59*). In addition, the absence of any discernible excess risk of leukemia among 263 children conceived shortly after the bombings whose fathers received a dose ≥10 mSv (average dose, 257 mSv) is inconsistent with the findings of Gardner et al. (*60*).

Subsequent to the publication of the results of Gardner et al., two large case–control studies were initiated. Kinlen et al. (*61*) found no association between recorded doses of paternal preconceptional irradiation and childhood leukemia and non-Hodgkin's lymphoma in a case–control study covering the whole of Scotland for 1958–1990. Similarly, in a case–control study of childhood leukemia cases born to mothers residing near nuclear facilities in Ontario and diagnosed during 1950-1988, no evidence of an increased risk due to recorded paternal preconceptional irradiation was found (*62*). This study also found no association with the dose received from monitored occupational exposures to tritium. Little (*63*) has demonstrated that the combined results of the Scottish and Ontario studies are incompatible with the findings of Gardner et al. at marginal levels of statistical significance (two-sided $p \cong 0.1$).

Recently, Michaelis et al. (*64*) have reported the results of a historical cohort study of children born to fathers working in the West German nuclear industry. They found no evidence for an increased risk of either childhood cancer or leukemia due to paternal preconceptional irradiation.

The results of Gardner et al. prompted a comprehensive investigation of cancer among the children of the male Sellafield workforce by the UK Health and Safety Executive (*65,66*). In a case–control study, conducted as part of this investigation, it was found that the association between childhood leukemia and non-Hodgkin's lymphoma and the recorded doses of radiation from external sources received by fathers over the entire preconceptional period is confined to children born in the village of Seascale. The strength of this association in Seascale is statistically incompatible with the absence of an association in children born outside this village. No occupational exposure examined could explain the confinement of the association to Seascale children. The association does not extend to childhood cancers other than leukemia and non-Hodgkin's lymphoma. (In fact, a negative association between cumulative preconceptional dose and other cancers was found.) The Health and Safety Executive study demonstrated that the original association reported by Gardner et al. concerning the 6-month preconceptional dose was an artifact of the *pro rata* doses obtained from annual dose summaries. This association with the 6-month dose was not replicated using original film badge records, nor was an association found with the dose received in the more biologically appropriate 12-week period before conception, whether or not the analysis was confined to Seascale-born subjects.

Using data from the report of the Health and Safety Executive, Little et al. (*67*) demonstrated that the Seascale association is not only incompatible in regard to the lack of an association for children of the Sellafield workforce born in the rest of West Cumbria, but also in regard to the absence of any association in the children of the Scottish and Ontario radiation workers and in the offspring of the Japanese atomic bomb survivors (Table 1). The Seascale association is inconsistent with the negative findings of all other epidemiological studies using objective measures of radiation dose.

Parker et al. (*68*) identified more than 9,000 children born in Cumbria during 1950–1989 whose fathers had received a radiation dose while employed at Sellafield before the child's conception. Over 90% of these children were born in West Cumbria outside Seascale, and the Seascale-born children accounted for only 7% of the collective dose of paternal preconceptional irradiation. This small fraction of the putative excess risk of childhood leukemia associated with the Seascale-born children is incompatible with an explanation of the Seascale excess in terms of paternal preconceptional irradiation, since many more leukemia cases should have occurred among the children of the Sellafield workforce born in the rest of West Cumbria (*68,69*). Draper et al. (*70*) demonstrated that the childhood leukemia excess in Seascale does not extend generally to the remainder of West Cumbria.

Further, Kinlen (*71*) found a statistically significant excess of childhood leukemia and non-Hodgkin's lymphoma among residents of Seascale who were born outside the village. This excess cannot be accounted for by recorded doses of paternal irradiation before conception. Therefore, the association with paternal preconceptional irradiation is not sufficient to account for the excess cases which have occurred in the village.

Both Little et al. (*67*) and Wakeford et al. (*72*) have examined the speculative suggestion that the confinement of the association between childhood leukemia and paternal preconceptional irradiation to children born in Seascale might be due to synergy between such exposure and some factor [possibly related to infection (*73,74*)] restricted to Seascale. Such an explanation is not viable because the interaction would have to be implausibly strong to account for the pronounced geographical confinement of the effect (*67*), and the initiating mutation rate required to predispose offspring to childhood leukemia would have to be so high as to be incredible (*72*). Further, synergy occurs between two factors which act independently to increase the risk of a disease (*75*), whereas no reliable evidence exists for paternal exposure to radiation before conception

Table 1. The relative risk of childhood leukemia associated with a 1 cSv cumulative dose of radiation received by a father before the conception of a child, derived from substantive studies using objective measures of radiation dose published since the report of Gardner et al. (*38*)[a]

Data set	Relative risk per 1cSv (95% CI)
Offspring of Sellafield workforce born in Seascale (*65,66*)	4.50 (2.33–8.20)
Offspring of Sellafield workforce born in the rest of West Cumbria (*65,66*)	1.03 (0.95–1.24)
Offspring of Ontario radiation workers (*62*)	0.96 (<0.93–1.24)
Offspring of Scottish radiation workers (*61*)	<0.95 (<0.95–1.20)
Offspring of Japanese atomic bomb survivors (*56*)	<1.00 (<1.00–1.01)

[a]After Little et al. (*67*), using a linear relative risk model.

having a leukemogenic effect in the absence of the "Seascale factor."

One suggestion made by Gardner et al. (*38*) is that doses of external radiation exposure might be acting as a surrogate for doses due to internally deposited radionuclides, an interpretation favored by Roman et al. (*46*). As noted by Nussbaum and Köhnlein (*1*), some support for this proposition was provided by Sorahan and Roberts (*76*) using data from the OSCC. They found an association between assessed potential for exposure to radionuclides and childhood cancers other than leukemia and non-Hodgkin's lymphoma, but not for leukemia and non-Hodgkin's lymphoma. However, the assessed potential for exposure to radionuclides was based solely on job descriptions provided at interview, and Sorahan et al. (*77*) have subsequently concluded that this association was due to information bias. (Interestingly, this latter study found no excess risk of childhood cancer or leukemia among offspring of radiologists or industrial radiographers.) Moreover, the Health and Safety Executive (*65,66*) found no association between childhood leukemia and non-Hodgkin's lymphoma or other childhood cancers and internal radiation doses to the testes, based upon biological monitoring data at Sellafield. This is consistent with the recent study of Andersson et al. (*78*), who found no excess risk of leukemia and non-Hodgkin's lymphoma or other cancers among the offspring of Danish patients given injections of the radioactive contrast medium Thorotrast, who were associated with an estimated average internal preconceptional dose to the testes of around 1 Sv.

The hypothesis generated by the study of Gardner et al. (*38*)—that exposure of fathers to radiation before the conception of their children leads to an increased risk of leukemia in these children—has not been supported by subsequent epidemiological studies and is inconsistent with the current understanding of radiation-induced adverse heritable effects (*34,79*). The heritable component of childhood leukemia is small [around 5% (*80*)], and the currently accepted risk coefficient for all hereditary effects implies that less than two excess cases of a severe hereditary disorder would be observed in children of the male Sellafield workforce compared with a "background" of around 340 cases among this number of children (*69*). A study of obstetric outcomes of pregnancies in women residing in Seascale found no evidence of an excess risk of adverse effects that might be related to heritable genetic damage (*81*), although this study was based on just 228 pregnancies.

The findings of Gardner et al. led to a lengthy court case heard in the High Court in London during 1992–1993. Many expert witnesses from around the world gave evidence in a 90-day hearing. The judge concluded that on the basis of the scientific evidence "the scales tilt decisively" against paternal preconceptional irradiation being the cause or a material contributory cause of the Seascale childhood leukemia excess (*82*). This conclusion is concordant with that of scientific authorities: a causal interpretation of the association between childhood leukemia and paternal preconceptional irradiation reported by Gardner et al. cannot be sustained (*13,83*).

Conclusions

The epidemiological evidence reviewed here does not indicate that the risk of childhood cancer arising from intrauterine irradiation or irradiation of parents before conception has been underestimated by national and international bodies responsible for assessing radiation risks. The risk coefficients associated with intrauterine irradiation which have been adopted by these committees are consistent with the results of the latest analyses of the OSCC data, contrary to the suggestion of Nussbaum and Köhnlein (*1*). No reliable support exists for the association between childhood leukemia and paternal preconceptional radiation dose, which has been found to be confined to the children born in the village of Seascale and which does not extend to other childhood cancers; the original association reported by Gardner et al. (*38,39*) seems most likely to have been a chance finding.

Doll (*84*) has reviewed the evidence from other epidemiological studies of groups exposed to low levels of ionizing radiation, particularly nuclear industry workers and populations exposed to nuclear weapons testing fallout. He concluded that the evidence from these studies is compatible with the risk coefficients derived by national and international scientific committees from the studies of those receiving higher doses, especially the Japanese atomic bomb survivors. This conclusion is consistent with the scientific evidence reviewed in this paper.

References

1. Nussbaum RH, Köhnlein W. Inconsistencies and open questions regarding low-dose health effects of ionizing radiation. Environ Health Perspect 102:656–667 (1994).
2. Stewart AM, Webb JW, Giles BD, Hewitt D. Malignant disease in childhood and diagnostic irradiation in utero. Lancet ii:447 (1956).
3. Stewart AM, Webb JW, Hewitt D. A survey of childhood malignancies. Br Med J i:1495–1508 (1958).
4. Stewart A, Kneale GW. Radiation dose effects in relation to obstetric x-rays and childhood cancers. Lancet i:1185–1188 (1970).
5. Bithell JF, Stewart AM. Prenatal irradiation and childhood malignancy: a review of British data from the Oxford Survey. Br J Cancer 31:271–287 (1975).
6. Totter JR, MacPherson HG. Do childhood cancers result from pre-natal x-rays? Health Phys 40:511–524 (1981).
7. Kneale GW, Stewart AM. Prenatal x-rays and cancers: further tests of data from the Oxford survey of childhood cancers. Health Phys 51:369–376 (1986).
8. Muirhead CR, Kneale GW. Prenatal irradiation and childhood cancer. J Radiol Prot 9:209–212 (1989).
9. MacMahon B. Prenatal x-ray exposure and childhood cancer. J Natl Cancer Inst 28:1173–1191 (1962).
10. Monson RR, MacMahon B. Prenatal x-ray exposure and cancer in children. In: Radiation carcinogenesis: epidemiology and biological significance (Boice JD Jr, Fraumeni JF Jr, eds). New York:Raven Press, 1984;97–105.
11. Bithell JF. Epidemiological studies of children irradiated *in utero*. In: Low dose radiation: biological bases of risk assessment (Baverstock KF, Stather JW, eds). London:Taylor and Francis, 1989;77–87.
12. Court Brown WM, Doll R, Bradford Hill A. Incidence of leukaemia after exposure to diagnostic radiation in utero. Br Med J ii:1539–1545 (1960).
13. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. New York:United Nations, 1994.
14. Hewitt D, Sanders B, Stewart A. Oxford survey of childhood cancers: progress report IV—Reliability of data reported by case and control mothers. Mon Bull Minist Health Lab Serv 25:80–85 (1966).
15. Mole RH. Antenatal irradiation and childhood cancer: causation or coincidence? Br J Cancer 30:199–208 (1974).
16. Harvey EB, Boice JD Jr, Honeyman M, Flannery JT. Prenatal x-ray exposure and childhood cancer in twins. N Engl J Med 312:541–545 (1985).
17. Rodvall Y, Pershagen G, Hrubec Z, Ahlbom A, Pedersen NL, Boice JD. Prenatal x-ray exposure and childhood cancer in Swedish twins. Int J Cancer 46:362–365 (1990).
18. Inskip PD, Harvey EB, Boice JD Jr, Stone BJ, Matanoski G, Flannery JT, Fraumeni JF Jr. Incidence of childhood cancer in twins. Cancer Causes Control 2:315–324 (1991).
19. Rodvall Y, Hrubec Z, Pershagen G, Ahlbom A, Bjurman A, Boice JD Jr. Childhood cancer among Swedish twins. Cancer Causes Control 3:527–532 (1992).
20. Graham S, Levin ML, Lilienfeld AM, Schuman LM, Gibson R, Dowd JE, Hempelmann LH. Preconception, intrauterine, and postnatal irradiation as related to leukemia. Natl Cancer Inst Monogr 19:347–371 (1966).
21. Gilman EA, Kneale GW, Knox EG, Stewart AM. Pregnancy x-rays and childhood cancers: effects of exposure age and radiation dose. J Radiol Prot 8:3–8 (1988).
22. Mole RH. Childhood cancer after prenatal

exposure to diagnostic x-ray examinations in Britain. Br J Cancer 62:152–168 (1990).
23. Knox EG, Stewart AM, Kneale GW, Gilman EA. Prenatal irradiation and childhood cancer. J Radiol Prot 7:177–189 (1987).
24. United Nations Scientific Committee on the Effects of Atomic Radiation. Genetic and somatic effects of ionizing radiation. New York:United Nations, 1986.
25. Benjamin SA, Lee AC, Angleton GM, Saunders WJ, Miller GK, Williams JS, Brewster RD, Long RI. Neoplasms in young dogs after perinatal irradiation. J Natl Cancer Inst 77:563–571 (1986).
26. Committee on the Biological Effects of Ionizing Radiations. Health effects of exposure to low levels of ionizing radiation, BEIR V. Washington DC:National Academy Press, 1990.
27. MacMahon B. Some recent issues in low-exposure radiation epidemiology. Environ Health Perspect 81:131–135 (1989).
28. Miller RW. Effects of prenatal exposure to ionizing radiation. Health Phys 59:57–61 (1990).
29. United Nations Scientific Committee on the Effects of Atomic Radiation. Ionizing radiation: levels and effects, vol II: effects. New York:United Nations, 1972.
30. Bithell JF, Stiller CA. A new calculation of the carcinogenic risk of obstetric x-raying. Stat Med 7:857–864 (1988).
31. Bithell JF. Statistical issues in assessing the evidence associating obstetric irradiation and childhood malignancy. In: Neue Bewertung des Strahlenriskos: Niedrigdosis-Strahlung und Gesundheit, proceedings, 1992, Kiel, Germany (Lengfelder E, Wendhausen H, eds). Munich:MMV Medizine Verlag, 1993;53–60.
32. Yoshimoto Y, Kato H, Schull WJ. Risk of cancer among children exposed in utero to A-bomb radiations, 1950–84. Lancet ii:665–669 (1988).
33. Straume T, Egbert SD, Woolson WA, Finkel RC, Kubik PW, Gove HE, Sharma P, Hoshi M. Neutron discrepancies in the DS86 Hiroshima dosimetry system. Health Phys 63:421–426 (1992).
34. Muirhead CR, Cox R, Stather JW, MacGibbon BH, Edwards AA, Haylock RGE. Estimates of late radiation risks to the UK population. Doc NRPB 4(4):15–157 (1993).
35. Stevens W, Thomas DC, Lyon JL, Till JE, Kerber RA, Simon SL, Lloyd RD, Elghany NA, Preston-Martin S. Leukemia in Utah and radioactive fallout from the Nevada test site. J Am Med Assoc 264:585–591 (1990).
36. Darby SC, Olsen JH, Doll R, Thakrar B, de Nully Brown P, Storm HH, Barlow L, Langmark F, Teppo L, Tulinius H. Trends in childhood leukaemia in the Nordic countries in relation to fallout from atmospheric nuclear weapons testing. Br Med J 304:1005–1009 (1992).
37. Independent Advisory Group. Investigation of the possible increased incidence of cancer in West Cumbria. London:Her Majesty's Stationery Office, 1984.
38. Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S, Terrell JD. Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. Br Med J 300:423–429 (1990).
39. Gardner MJ. Fathers occupational exposure to radiation and the raised level of childhood leukemia near the Sellafield nuclear plant. Environ Health Perspect 94:5–7 (1991).
40. Gardner MJ. Paternal occupations of children with leukaemia. Br Med J 305:715 (1992).
41. Abrahamson S. Childhood leukemia at Sellafield. Radiat Res 123:237–238 (1990).
42. Neel JV. Update on the genetic effects of ionizing radiation. J Am Med Assoc 266:698–701 (1991).
43. Evans HJ. Ionising radiations from nuclear establishments and childhood leukaemias—an enigma. BioEssays 12:541–549 (1990).
44. Urquhart JD, Black RJ, Muirhead MJ, Sharp L, Maxwell M, Eden OB, Adams Jones D. Case-control study of leukaemia and non-Hodgkin's lymphoma in children in Caithness near the Dounreay nuclear installation. Br Med J 302:687–692, 818 (1991).
45. Little MP. A comparison of the risks of childhood leukaemia from parental pre-conception exposure to radiation in the Sellafield and Dounreay workforces and the Japanese bomb survivors. J Radiol Prot 11:231–240 (1991).
46. Roman E, Watson A, Beral V, Buckle S, Bull D, Baker K, Ryder H, Barton C. Case-control study of leukaemia and non-Hodgkin's lymphoma among children aged 0–4 years living in West Berkshire and North Hampshire health districts. Br Med J 306:615–621 (1993).
47. McKinney PA, Alexander FE, Cartwright RA, Parker L. Parental occupations of children with leukaemia in west Cumbria, north Humberside, and Gateshead. Br Med J 302:681–687 (1991).
48. Alexander FE, Cartwright RA, McKinney PA. Paternal occupations of children with leukaemia. Br Med J 305:715–716 (1992).
49. Rose KSB. Pre-1989 epidemiological surveys of low-level dose pre-conception irradiation. J Radiol Prot 10:177–184 (1990).
50. Shu XO, Gao YT, Brinton LA, Linet MS, Tu JT, Zheng W, Fraumeni JF. A population-based case-control study of childhood leukemia in Shanghai. Cancer 62:635–644 (1988).
51. Shu XO, Jin F, Linet MS, Zheng W, Clemens J, Mills J, Gao YT. Diagnostic x-ray and ultrasound exposure and risk of childhood cancer. Br J Cancer 70:531–536 (1994).
52. Shu XO, Reaman GH, Lampkin B, Sather HN, Pendergrass TW, Robison LL. Association of paternal diagnostic x-ray exposure with risk of infant leukemia. Cancer Epidemiol Biomarkers Prev 3:645–653 (1994).
53. Shiono PH, Chung CS, Myrianthopoulos NC. Preconception radiation, intrauterine diagnostic radiation, and childhood neoplasia. J Natl Cancer Inst 65:681–686 (1980).
54. Graham S, Levin ML, Lilienfeld AM, Dowd JE, Schuman LM, Gibson R, Hempelmann LH, Gerhardt P. Methodological problems and design of the tri-state leukemia survey. Ann NY Acad Sci 107:557–569 (1963).
55. Kneale GW, Stewart AM. Pre-conception x-rays and childhood cancers. Br J Cancer 41:222–226 (1980).
56. Yoshimoto Y, Neel JV, Schull WJ, Kato H, Soda M, Eto R, Mabuchi K. Malignant tumors during the first 2 decades of life in the offspring of atomic bomb survivors. Am J Hum Genet 46:1041–1052 (1990).
57. Little MP. A comparison between the risks of childhood leukaemia from parental exposure to radiation in the Sellafield workforce and those displayed among the Japanese bomb survivors. J Radiol Prot 10:185–198 (1990).
58. Little MP. The risks of leukaemia and non-cancer mortality in the offspring of the Japanese bomb survivors and a comparison of leukaemia risks with those in the offspring of the Sellafield workforce. J Radiol Prot 12:203–218 (1992).
59. Little MP, Wakeford R, Charles MW. An analysis of leukaemia, lymphoma and other malignancies together with certain categories of non-cancer mortality in the first generation offspring (F_1) of the Japanese bomb survivors. J Radiol Prot 14:203–218 (1994).
60. Little MP. A comparison of the apparent risks of childhood leukaemia from parental exposure to radiation in the six months prior to conception in the Sellafield workforce and the Japanese bomb survivors. J Radiol Prot 11:77–90 (1991).
61. Kinlen LJ, Clarke K, Balkwill A. Paternal preconceptional radiation exposure in the nuclear industry and leukaemia and non-Hodgkin's lymphoma in young people in Scotland. Br Med J 306:1153–1158 (1993).
62. McLaughlin JR, King WD, Anderson TW, Clarke EA, Ashmore JP. Paternal radiation exposure and leukaemia in offspring: the Ontario case-control study. Br Med J 307:959–966, 1257, 1462 (1993).
63. Little MP. A comparison of the risks of leukaemia in the offspring of the Japanese bomb survivors and those of the Sellafield workforce with those in the offspring of the Ontario and Scottish workforces. J Radiol Prot 13:161–175 (1993).
64. Michaelis J, Kaatsch P, Zöllner I. Querschnittsuntersuchung zur Häufigkeit von Krebserkrankungen bei Kindern von beruflich strahlenexponierten Beschäftigten in westdeutschen kerntechnischen Anlagen. Arbeitsmed Sozialmed Umweltmed 29:324–335 (1994).
65. Health and Safety Executive. HSE investigation of leukaemia and other cancers in the children of male workers at Sellafield. Sudbury, UK:HSE Books, 1993.
66. Health and Safety Executive. HSE investigation of leukaemia and other cancers in the children of male workers at Sellafield: review of results published in October 1993. Sudbury, UK:HSE Books, 1994.
67. Little MP, Wakeford R, Charles MW. A comparison of the risks of leukaemia in the offspring of the Sellafield workforce born in Seascale and those born elsewhere in West Cumbria with the risks in the offspring of the Ontario and Scottish workforces and the Japanese bomb survivors. J Radiol Prot 14:187–201 (1994).
68. Parker L, Craft AW, Smith J, Dickinson H, Wakeford R, Binks K, McElvenny D, Scott L, Slovak A. Geographical distribution of preconceptional radiation doses to fathers employed at the Sellafield nuclear installation, West Cumbria. Br Med J 307:966–971 (1993).
69. Wakeford R, Tawn EJ, McElvenny DM, Scott E, Binks K, Parker L, Dickinson H, Smith J. The descriptive statistics and health implications of occupational radiation doses received by men at the Sellafield nuclear installation before the conception of their children. J Radiol Prot 14:3–16 (1994).
70. Draper GJ, Stiller CA, Cartwright RA, Craft AW, Vincent TJ. Cancer in Cumbria and in the vicinity of the Sellafield nuclear installation, 1963–90. Br Med J 306:89–94 (1993).
71. Kinlen LJ. Can paternal preconceptional radiation account for the increase of leukaemia and non-Hodgkin's lymphoma in Seascale? Br Med J 306:1718–1721 (1993).
72. Wakeford R, Tawn EJ, McElvenny DM, Binks K, Scott LE, Parker L. The Seascale childhood

leukaemia cases—the mutation rates implied by paternal preconceptional radiation doses. J Radiol Prot 14:17–24 (1994).
73. Kinlen LJ. Epidemiological evidence for an infective basis in childhood leukaemia. Br J Cancer 71:1–5 (1995).
74. Kinlen LJ, Dickson M, Stiller CA. Childhood leukaemia and non-Hodgkin's lymphoma near large rural construction sites, with a comparison with Sellafield nuclear site. Br Med J 310:763–768 (1995).
75. Blot WJ, Day NE. Synergism and interaction—are they equivalent? Am J Epidemiol 110:99–100 (1979).
76. Sorahan T, Roberts PJ. Childhood cancer and paternal exposure to ionizing radiation: preliminary findings from the Oxford survey of childhood cancers. Am J Ind Med 23:343–354 (1993).
77. Sorahan T, Lancashire RJ, Temperton DH, Heighway P. Childhood cancer and paternal exposure to ionizing radiation: a second report from the Oxford survey of childhood cancers. Am J Ind Med 28:71–78 (1995).
78. Andersson M, Juel K, Ishikawa Y, Storm HH. Effects of preconceptional irradiation on mortality and cancer incidence in the offspring of patients given injections of Thorotrast. J Natl Cancer Inst 86:1866–1870 (1994).
79. United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation. New York:United Nations, 1993.
80. Hawkins MM, Draper GJ, Winter DL. Cancer in the offspring of survivors of childhood leukaemia and non-Hodgkin lymphomas. Br J Cancer 71:1335–1339 (1995).
81. Jones KP, Wheater AW. Obstetric outcomes in West Cumberland Hospital: is there a risk from Sellafield? J R Soc Med 82:524–527 (1989).
82. Wakeford R, Tawn EJ. Childhood leukaemia and Sellafield: the legal cases. J Radiol Prot 14:293–316 (1994).
83. Doll R, Evans HJ, Darby SC. Paternal exposure not to blame. Nature 367:678–680 (1994).
84. Doll R. Epidemiological evidence of effects of small doses of ionising radiation with a note on the causation of clusters of childhood leukaemia. J Radiol Prot 13:233–241 (1993).